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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,478	06/07/99	BRANTON	P 50013/002003

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KRISTINA BIEKER BRADY
CLARK & ELBING
176 FEDERAL STREET
BOSTON MA 02110

EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	16

DATE MAILED: 10/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/214,478	BRANTON ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7-23-01.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment and declarations filed 7-23-01 have been entered. Claims 1-60 and 64-80 have been canceled. Claims 81-100 have been added. Claims 81-100 are pending and under consideration.

Oath/Declaration

1. The oath or declaration remains defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MEP. §§ 602.01 and 602.02.

The oath or declaration is defective because:

There is no signature of the inventor Josee N Lavoie.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 81-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. Claims 81-100 are newly added claims and applicants' amendment filed 7-23-01 necessitates this new ground of rejection.

Claims 81-87 are directed to a method of inducing apoptosis of a cell, such as a cancer cell, comprising expressing in said cell a nucleic acid, such as an adenoviral vector or retroviral vector, having at least 50%, 75%, or 90% identity to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, wherein said nucleic acid is operatively linked to a constitutive, inducible, or cell-type specific heterologous regulatory sequence and encodes a polypeptide capable of inducing apoptosis. Claims 88-93 and 95-100 are directed to a pharmaceutical composition comprising the nucleic acid set forth above, and an expression vector comprising said nucleic acid. Claim 94 is directed to a pharmaceutical composition comprising a nucleic acid that hybridizes to complement of SEQ ID No. 3 at high stringency or is at least 50% identical to SEQ ID No. 3 and further encodes a polypeptide having a conservative amino acid substitution relative to SEQ ID No. 4.

The specification of the present application only discloses adenovirus nucleotide sequences SEQ ID Nos. 1 and 3 encoding E4orf6 (SEQ ID No. 2) and E4orf4 (SEQ ID No. 4) polypeptides, respectively. The claims encompass any nucleic acid that is at least 50%, 75%, or 90% identical to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, or further encodes a polypeptide having a conservative amino acid substitution relative to SEQ ID No. 4.

Any nucleic acid that hybridizes to the complement of SEQ ID No. 3 at high stringency reads on adding unknown nucleotide sequence at 5' end, 3' end, or within the nucleotide sequence of SEQ ID No. 3 and therefore encompass unrelated or unidentified gene which contains sequence that differs dramatically from the polynucleotide sequence of SEQ ID No. 3 as disclosed in the instant application. The claims encompass variant structures of different nucleic acids, and in the present state of the art the structure of one does not provide guidance to the structure of the others. The common attributes of the nucleic acid that hybridizes to the complement of SEQ ID No. 3 at high stringency are not described. The claims also encompass any mRNA that encodes any polypeptide that can induce apoptosis, and thus include unknown and unidentified mRNA sequences from other genes.

Similarly, any nucleic acid having at least 50%, 75%, or 90% identity to the sequence of SEQ ID No. 3, or further encodes a polypeptide having a conservative amino acid substitution relative to SEQ ID No. 4 reads on unrelated or unidentified gene which contains sequence that differs dramatically from the polynucleotide sequence of SEQ ID No. 3 as disclosed in the instant application. The claims encompass unrelated or unidentified nucleotide sequence at the 5' and 3' end or within the claimed nucleic acid sequence of SEQ ID No. 3. The claims encompass variant structures of different polynucleotides, and in the present state of the art the structure of one does not provide guidance to the structure of the others. The common attributes of any nucleic acid having at least 50%, 75%, or 90% identity to the sequence of SEQ ID No. 3 and still encoding a polypeptide capable of inducing apoptosis are not described. The claims also encompass any

mRNA having at least 50%, 75%, or 90% identity to the sequence of SEQ ID No. 3, and thus include unknown and unidentified mRNA sequences from other genes.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed nucleic acid sequences SEQ ID Nos. 1 and 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Thus, one of skill in the art would conclude that applicant was not in possession of the claimed composition comprising the nucleic acid set forth above or a method of using said nucleic acid because a description of only one member is not representative of the variants and is insufficient to support the claim.

4. Claims 81-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating apoptosis *in vitro* by using a plasmid comprising nucleotide sequence of the disclosed SEQ ID No. 1 or 3 encoding E4orf6 or E4orf4, does not reasonably provide enablement for any pharmaceutical composition or expression vector comprising the nucleic acid set forth above, and a method of using said nucleic acid to induce apoptosis of any cell *in vitro* or *in vivo* other than the disclosed E4orf4 or E4orf6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Claims 81-100 are newly added claims and applicants' amendment filed 7-23-01 necessitates this new ground of rejection.

Claims 81-87 are directed to a method of inducing apoptosis of a cell, such as a cancer cell, comprising expressing in said cell a nucleic acid, such as an adenoviral vector or retroviral vector, having at least 50%, 75%, or 90% identity to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, wherein said nucleic acid is operatively linked to a constitutive, inducible, or cell-type specific heterologous regulatory sequence and encodes a polypeptide capable of inducing apoptosis. Claims 88-93 and 95-100 are directed to a pharmaceutical composition comprising the nucleic acid set forth above, and an expression vector comprising said nucleic acid. Claim 94 is directed to a pharmaceutical composition comprising a nucleic acid that hybridizes to complement of SEQ ID No. 3 at high stringency or is at least 50% identical to SEQ ID No. 3 and further encodes a polypeptide having a conservative amino acid substitution relative to SEQ ID No. 4.

The specification of the present application only discloses stimulating apoptosis *in vitro* by using a plasmid comprising nucleotide sequence of the disclosed SEQ ID No. 1 or 3 encoding E4orf6 or E4orf4. The claims encompass any nucleic acid that is at least 50%, 75%, or 90% identical to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, or further encodes a polypeptide having a conservative amino acid substitution relative to SEQ ID No. 4 and said nucleic acid encodes a polypeptide capable of inducing apoptosis, and a method of using said nucleic acid to induce apoptosis in a cell *in vitro* or *in vivo*.

The polypeptide sequences encoded by the nucleic acid set forth above represent polypeptides encoded by different genes and their variants and could vary dramatically from

E4orf4 or E4orf6 polypeptide. The amino acid sequence of a protein determines its structural and functional properties (including half-life), and predictability of whether the polypeptide sequences encoded by the nucleic acid set forth above would still retain the activity of inducing apoptosis *in vitro* or *in vivo* is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger (Peptide Hormones, 1976) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). In view of the unpredictability of the biological function of a protein from mere polypeptide sequence, it would be unpredictable whether the polypeptide sequences encoded by the nucleic acid set forth above would have the activity of inducing apoptosis *in vitro* or *in vivo* within the targeted cells. One skilled in the art would not know how to use the full scope of the claimed nucleic acid to induce apoptosis in the targeted cells *in vitro* or *in vivo*.

Further, the term "pharmaceutical composition" implies production of therapeutic effect of said composition for a particular disease or disorder of a subject *in vitro* and *in vivo*. Therefore, claims 81-94 read on gene therapy using nucleic acid set forth above for a particular disease or disorder *in vivo*. The specification fails to provide adequate guidance and evidence for the correlation between the nucleic acid set forth above and the particular disease or disorder to be treated using said nucleic acid. The specification also fails to provide adequate guidance and evidence for the type of vector and promoter used, the administration routes of said vector, and

whether introduction of the vector containing the nucleic acid set forth above into a subject including humans, mammals, insects, fishes etc. would provide sufficient expression of a polypeptide capable of inducing apoptosis in the targeted cells such as to exhibit therapeutic effect for a particular disease or disorder of a subject *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated

with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Further, Eck et al. (Pharmacological Basis of Therapeutics, 1996) indicates that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e.g. bridging pages 81-82). It is unclear whether introduction of the nucleic acid set forth above into a subject including humans, mammals, insects, fishes etc. would provide sufficient expression of the polypeptide capable of inducing apoptosis in the targeted cells such as to exhibit therapeutic effect for a particular disease or disorder of a subject *in vivo*. One skilled in the art would not know how to use the

nucleic acid set forth above to induce apoptosis for a particular disease or disorder of a subject *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require a skilled artisan undue experimentation at the time of the invention to practice over the full scope of the invention claimed.

Applicants argue that the specification describe various vectors and method of their use for expressing foreign genes in cell *in vivo* were known in the art (amendment, page 9), and the declaration of Dr. Branton has shown the expression of E4orf4 resulted in reduced tumor growth relative to control mice *in vivo* (amendment, page 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-18-01 (Paper No. 13) and the reasons set forth above.

Applicants argue that Dr Branton's declaration shows the nucleotide sequence of Ad9, Ad12 and Ad40 encoding E4orf4, which share 53%, 51%, and 48% identity with Ad2 E4orf4, and their E4orf4 polypeptides induce apoptosis. Applicants further argue that various mutations of E4orf4 polypeptide do not alter E4orf4 biological activity (amendment, page 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-18-01 (Paper No. 13) and the reasons set forth above and that the scope of the claims is much broader than just a few adenoviral serotypes or just a few mutations within the Ad2 E4orf4 polypeptide.

Further, it is unclear what E4orf4 biological activity of the various mutant E4orf4 is referred to in the declaration (page 5) and it is also unclear whether these mutant E4orf4 polypeptides could induce apoptosis *in vivo*.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 88-92 and 95-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohgi et al., 1991 (J. Biochem. Vol. 109, p. 776-785) in view of Chrobozek et al., GenEmbl Accession No. M73260 (4-8-1996). Claims 88-92 and 95-99 are newly added claims and applicants' amendment filed 7-23-01 necessitates this new ground of rejection.

Claims 88-92 and 95-99 are directed to a pharmaceutical composition comprising a nucleic acid, having at least 50%, 75%, or 90% identity to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, wherein said nucleic acid is operatively linked to a constitutive, inducible, or cell-type specific heterologous regulatory sequence and encodes a polypeptide capable of inducing apoptosis, and an expression vector comprising said nucleic acid.

Ohgi teaches preparation of a composition containing a vector comprising RNaseRh cDNA, transfection of yeast host cells with said vector, and purification of the recombinant RNaseRh protein from said yeast host cells (e.g. p. 777). The **GAPDH gene promoter** used by Ohgi in the expression plasmid vector for RNase Rh is **heterologous to the RNase Rh protein** to be expressed. The term "pharmaceutical" in the claims does not carry weight in the 103 rejection. The buffer solution containing the vector comprising RNaseRh cDNA is considered a pharmaceutically acceptable carrier. Ohgi does not teach the presence of nucleotide sequence SEQ ID No. 3 encoding a polypeptide capable of inducing apoptosis.

Chroboczek discloses a nucleotide sequence, GenEmbl Accession No. M73260, which is 100% identical to SEQ ID No. 3 (E4orf4), therefore, said nucleotide sequence would encode the amino acid sequence of SEQ ID No. 4 (E4orf4) polypeptide. It would be inherent to the polypeptide sequence encoded by the nucleotide sequence disclosed by Chroboczek to induce apoptosis because said polypeptide sequence is 100% identical to E4orf4 polypeptide.

It would have been obvious for one ordinary skill at the time of the invention to substitute the RNaseRh cDNA with the nucleotide sequence taught by Chroboczek to construct a vector and a host cell containing said vector as taught by Ohgi because both the RNase Rh cDNA and the nucleotide sequence of GenEmbl Accession No. M73260 are DNA fragments and it is general knowledge to replace one DNA fragment with another in an expression plasmid.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to produce and purify the recombinant polypeptide encoded by the nucleotide sequence disclosed by Chroboczek and to study the function of said protein as taught by Ohgi.

Applicants argue that the cited references Ohgi and Chroboczek do not teach or suggest using heterologous regulatory sequence and no function related to mammalian cells was ascribed to E4orf4 (amendment, page 14). This is not found persuasive because of the **GAPDH gene promoter** used by Ohgi in the expression plasmid vector for RNase Rh is **heterologous to the RNase Rh protein** to be expressed and it would be inherent to the polypeptide sequence encoded by the nucleotide sequence disclosed by Chroboczek to induce apoptosis because said polypeptide sequence is 100% identical to E4orf4 polypeptide as discussed above. Further, production of a recombinant protein using a host cell expressing said protein would be sufficient motivation for one of ordinary skill in the art.

7. Claims 88-92 and 95-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swinkels et al., 1993 (Antonie Van Leeuwenhoek, Vol. 64, p. 187-201) in view of Chrobozek et

al., GenEmbl Accession No. M73260 (4-8-1996). Claims 88-92 and 95-99 are newly added claims and applicants' amendment filed 7-23-01 necessitates this new ground of rejection.

Claims 88-92 and 95-99 are directed to a pharmaceutical composition comprising a nucleic acid, having at least 50%, 75%, or 90% identity to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, wherein said nucleic acid is operatively linked to a constitutive, inducible, or cell-type specific heterologous regulatory sequence and encodes a polypeptide capable of inducing apoptosis, and an expression vector comprising said nucleic acid.

Swinkels teaches various promoters and expression systems could be used in the dairy yeast Kluyveromyces lactis host cells for heterologous gene expression. Heterologous gene expression is of considerable interest for the production of pharmaceutical proteins of human origins, such as interferons or interleukins, and also in the area of industrial enzyme production (e.g. introduction, table 2). The listed S. Cerevisiae PGK promoter is heterologous to the yeast host K. Lactis and also is heterologous to the gene to be expressed in said K. Lactis host cells. The term "pharmaceutical" in the claims does not carry weight in the 103 rejection. The buffer solution containing the expression system is considered a pharmaceutically acceptable carrier. Swinkels does not teach the presence of nucleotide sequence SEQ ID No. 3 encoding a polypeptide capable of inducing apoptosis.

Chroboczek discloses a nucleotide sequence, GenEmbl Accession No. M73260, which is 100% identical to SEQ ID No. 3 (E4orf4), therefore, said nucleotide sequence would encode the

amino acid sequence of SEQ ID No. 4 (E4orf4) polypeptide. It would be inherent to the polypeptide sequence encoded by the nucleotide sequence disclosed by Chroboczek to induce apoptosis because said polypeptide sequence is 100% identical to E4orf4 polypeptide.

It would have been obvious for one ordinary skill at the time of the invention to substitute the heterologous gene with the nucleotide sequence taught by Chroboczek to construct a vector and a host cell containing said vector as taught by Swinkels because both the heterologous gene and the nucleotide sequence of GenEmbl Accession No. M73260 are DNA fragments and it is general knowledge to replace one DNA fragment with another in an expression plasmid.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to produce and purify the recombinant polypeptide encoded by the nucleotide sequence disclosed by Chroboczek for the pharmaceutical use as taught by Swinkels.

8. Claims 93 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swinkels et al., 1993 (Antonie Van Leeuwenhoek, Vol. 64, p. 187-201) in view of Chrobozek et al., GenEmbl Accession No. M73260 (4-8-1996) and Miller et al., 1995 (The FASEB Journal, Vol. 9, p.190-199). Claims 93 and 100 are newly added claims and applicants' amendment filed 7-23-01 necessitates this new ground of rejection.

Claims 93 and 100 are directed to a pharmaceutical composition comprising a nucleic acid, such as adenoviral or retroviral vector, having at least 50% identity to SEQ ID No. 3, or hybridizes to complement of SEQ ID No. 3 at high stringency, wherein said nucleic acid is

operatively linked to a constitutive, inducible, or cell-type specific heterologous regulatory sequence and encodes a polypeptide capable of inducing apoptosis, and an expression vector comprising said nucleic acid.

Swinkels teaches various promoters and expression systems could be used in the dairy yeast Kluyveromyces lactis host cells for heterologous gene expression. Heterologous gene expression is of considerable interest for the production of pharmaceutical proteins of human origins, such as interferons or interleukins, and also in the area of industrial enzyme production (e.g. introduction, table 2). The listed S. Cerevisiae PGK promoter is heterologous to the yeast host K. Lactis and also is heterologous to the gene to be expressed in said K. Lactis host cells. The term "pharmaceutical" in the claims does not carry weight in the 103 rejection. The buffer solution containing the expression system is considered a pharmaceutically acceptable carrier.

Swinkels does not teach the presence of nucleotide sequence SEQ ID No. 3 encoding a polypeptide capable of inducing apoptosis and the use of adenoviral or retroviral vector.

Chroboczek discloses a nucleotide sequence, GenEmbl Accession No. M73260, which is 100% identical to SEQ ID No. 3 (E4orf4), therefore, said nucleotide sequence would encode the amino acid sequence of SEQ ID No. 4 (E4orf4) polypeptide. It would be inherent to the polypeptide sequence encoded by the nucleotide sequence disclosed by Chroboczek to induce apoptosis because said polypeptide sequence is 100% identical to E4orf4 polypeptide.

Miller teaches construction of molecular conjugate vectors containing a plasmid DNA coupled to a ligand with cell or tissue affinity, retroviral, or adenoviral vectors comprising a

therapeutic gene under the control of a cellular promoter, such as a tissue-specific regulatory element, and use of said vectors for gene delivery of said therapeutic gene to targeted cells for the expression of said gene and treatment of a disease in a subject (e.g. p. 190, 192, 194, 195).

It would have been obvious for one ordinary skill at the time of the invention to substitute the heterologous gene with the nucleotide sequence taught by Chroboczek to construct an adenovrial or retroviral vector and a host cell containing said vector as taught by Swinkels and Miller because both the heterologous gene and the nucleotide sequence of GenEmbl Accession No. M73260 are DNA fragments and it is general knowledge to replace one DNA fragment with another in an expression plasmid.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to produce and purify the recombinant polypeptide encoded by the nucleotide sequence disclosed by Chroboczek for the pharmaceutical use as taught by Swinkels or to use the viral vectors for gene delivery of the nucleotide sequence disclosed by Chroboczek to targeted cells for expression and treatment of a disease in a subject as taught by Miller.

It should be noted that the Chroboczek reference was sent out but not included in the PTO-892 form by mistake. A courtesy copy is attached and the reference will be included in the PTO-892 form.

Conclusion

No claims is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Shin-Lin Chen, Ph.D.